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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

NOVEMBER 1944

THE PRACTICAL MANAGEMENT OF HYPERTENSION*

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WHEN a physician is called upon to take care of a patient with hypertension his first problem is to try to account for the hypertension on the basis of one of the known causes of hypertension. There are many such conditions but, for the most part, they are uncommon or rare. Nevertheless the possibility of one of these conditions being present must be kept in mind and they must be carefully ruled out before one may classify a case as one of essential hypertension or, in other words, as being of unknown etiology. The most important of these conditions to be looked for are glomerulonephritis, pyelonephritis, polycystic kidneys, hydronephrosis, congenital anomalies of the kidney and tumors of the adrenal glands.

UNILATERAL RENAL DISEASE

Especially important to rule out is the presence of a unilateral renal lesion. The interest which has been shown of late in this group of unilateral renal lesions as a possible basis for hypertension and the pos-

* A Friday Afternoon Lecture, April 7, 1944 at The New York Academy of Medicine.

sibility of cure by nephrectomy stems from the observation of Goldblatt that hypertension can be produced in animals by clamping the main artery of one kidney while leaving the other kidney intact and that removal of the treated kidney leads to a prompt fall in the blood pressure, provided the hypertension has not persisted too long.

It should be emphasized that all unilateral renal diseases do not lead to hypertension and that most of those renal conditions which do lead to hypertension are bilateral rather than unilateral. Furthermore, in those cases in which the renal lesion is unilateral, there is no way of knowing for certain which kidney is responsible for the hypertension. Cases in which the possibility of a unilateral renal lesion as the cause of the hypertension is suspected should be studied by all the indicated methods such as intravenous urography, and if necessary retrograde pyelography, cystoscopy and urine cultures. Two difficulties that stand in the way of this method are that we have no way of identifying with certainty the offending kidney and that removal of any normal tissue from a hypertensive patient may aggravate rather than improve the hypertension.

The chance for successful treatment by unilateral nephrectomy is greatest in young people and in those in whom the hypertension has not existed long enough to produce secondary changes in the heart, peripheral vessels and the other kidney.

At the Mayo Clinic, Braasch, Walters and Hammer studied 1,684 patients who were subjected to renal surgical procedures. They found that the renal lesion amenable to surgical treatment which occurs most often in association with hypertension is atrophic pyelonephritis. Hypertension occurred in 20 of 43 patients operated upon for primary atrophic pyelonephritis, or 46.5 per cent. Hypertension was observed in 20.3 per cent of 793 cases in which operation was performed for renal stone and in 14 per cent of 372 cases of hydronephrosis without stone. Hypertension was observed less frequently in the presence of renal tuberculosis than in most other forms of surgical kidney. It was present in 7.6 per cent of the 158 cases studied. Hypertension was found in 27.7 per cent of 137 cases in which operation was performed for renal adenocarcinoma.

It was found that the hypertension was relieved in approximately 70 per cent of cases of atrophic pyelonephritis, in 50 per cent of cases with renal tuberculosis and in 25 per cent of cases associated with renal

calculus, hydronephrosis or tumor.

Although the hypertension associated with surgical lesions of the kidneys is relieved more often by nephrectomy than by conservative operations, the blood pressure often returns to normal after nephrolithotomy and renal drainage. Hypertension alone is not sufficient reason for sacrificing a kidney with a calculus which is easily removable, or a hydronephrosis which might be corrected by a plastic operation, or a cortical infection which is amenable to chemotherapy and drainage. A good rule of thumb is that in patients with hypertension and unilateral renal lesions nephrectomy is indicated only if that would be the procedure of choice without reference to the hypertension.

Course and Prognosis

After having made certain that the patient whom you are studying has none of the conditions known to cause hypertension you may label him as having essential hypertension and this diagnosis will be applicable in about 95 per cent of hypertensions. It will be found very helpful when beginning to take care of such a case to have clearly in mind what usually happens to such cases and then to determine what is likely to happen to the particular case you are dealing with. You should take stock of the patient, appraise the physical status, estimate how much damage has already been done and then try to evaluate the further course.

It appears certain that essential hypertension is an hereditary disease and that hypertensives are born with the hypertensive trait. Many years may pass before hypertension appears but even during this prehypertensive period the tendency can be shown by a positive response to the cold pressor test. The next phase in the evolution of the disease is the period of intermittent hypertension when the elevated pressure may be present under stress or excitement, only to return spontaneously to a relatively normal pressure. Finally there is the phase of permanent hypertension. Obviously the clinical picture and the prognosis too will vary considerably depending upon which phase in the natural evolution of the disease the patient is in when seen.

Some of these patients who are picked up as a chance finding are completely free of symptoms, and may run a course of twenty to thirty years and die of some wholly unrelated condition. Others run a malignant course with very distressing symptoms and die within a

year or two of the onset. And in between these two extremes are the vast majority of hypertensives who run their course in about ten to fifteen years and who die of one of the effects of hypertension. On first seeing a patient we cannot know into which of these groups he should be placed. It is only after months of observation that we may get some idea of the outlook by observing the rate of progression of the disease, the changes occurring in the various organs and the response to therapy.

Before proceeding further let us see what ultimately happens to these patients. There are good statistical studies which show the cause of death in large series of these cases. The study of Bell and Clawson on 420 patients is fairly representative. They found the cause of death to be myocardial insufficiency in 45 per cent, coronary disease in 15 per cent, cerebral hemorrhage and thrombosis in 19 per cent, renal insufficiency in 9 per cent and accident or intercurrent disease in 12 per cent. So that taking together the cases of congestive failure and the cases of coronary disease the heart was the cause of death in 60 per cent of all cases. (Here, then, is one place where the physician can render genuine help with medical treatment.)

The data which we need in order to evaluate the prognosis in a patient may be grouped under the following headings:

1. *The level of the arterial pressure and its lability.* In general the prognosis is worse the higher the pressure, the height of the diastolic pressure being even more significant than the height of the systolic pressure. It is surprising though to find how often high levels of pressure such as 200–225 systolic, and 110–120 diastolic, are borne without symptoms for years. Nevertheless, one should regard any patient whose systolic pressure is over 250 and whose diastolic pressure is over 150 as definitely in danger.

Quite aside from the height of the pressure, if it remains at a fixed level, the prognosis is generally thought to be worse than when it fluctuates from day to day or hour to hour, or as influenced by sedatives, etc.

2. *The cardiovascular status:* A careful history will often reveal some evidence of *diminished cardiac reserve,* such as dyspnea on exertion or swelling of the feet at night. These symptoms may be very slight, give no serious discomfort and unless specifically enquired for may not be related by the patient.

Hypertrophy of the left ventricle should be looked for by physical examination and x-ray. During the early stages when the hypertrophy is of the concentric type and before dilatation occurs it may be difficult to detect, but even then it may be suspected on the x-ray by the shape of the cardiac silhouette with its accentuation of the cardiovascular angle and a rounding and elevation of the cardiac apex. The electrocardiogram, too, may provide evidence of left ventricular hypertrophy, when there is left deviation of the electrical axis, especially if the patient is a young adult.

Changes in the coronary arteries are suggested by anginal pain and by electrocardiographic changes.

Atherosclerosis of the aorta should be looked for. It presents a characteristic picture on x-ray with elongation, tortuosity, increased density and calcification.

3. *The renal status* should be carefully studied. The renal function is usually unimpaired until relatively late in the disease when the arteriolar sclerosis has led to extensive atrophy of the renal parenchyma. The concentrating power which is a measure of renal tubular function should be determined by any of the well established specific gravity tests. This is more sensitive than the clearance tests to slight degrees of renal damage, and therefore, if the concentration test is normal, one need not measure the clearance. But if the specific gravity is low, a clearance must be done to find out whether it is in the range of 30-40 per cent, which might be consistent with a subjectively well and active condition for several years; or whether the clearance is below 10 per cent with uremia due in a short time. When the clearance falls to 5 per cent of normal the clinical condition of uremia is either present or imminent.

In malignant nephrosclerosis the necrotic lesions in the renal arterioles cause rapid destruction of the kidney parenchyma with decreased function and uremia. In the absence of these necrotic lesions and in otherwise uncomplicated cases only a very small percentage go on to renal insufficiency.

Having determined the state of the heart, blood vessels and kidneys there is one additional fact which we should like to have in judging the outlook in any patient. That is the *duration of the hypertension* up to the time when the patient is first seen. Since the disease runs a long course in the average case, it is obvious that the earlier in the course

he is seen the longer he is likely to last, and the converse is also true. In the occasional patient who has been examined at regular intervals the approximate date of onset of the hypertension may be known; but in most cases, where the presence of hypertension is discovered by chance, it is only by indirect evidence that we may know something about how long it has been present. Such evidence is supplied by the data which I suggested that you collect about the level of the blood pressure and its lability, left ventricular hypertrophy, the anginal syndrome and coronary artery changes as evidenced by electrocardiogram, and atherosclerosis of the aorta as shown by x-ray. If all these data suggest that the hypertension is recent the outlook may confidently be predicted to be good, with the reservation always that an occasional hypertensive, especially those in the age group below 50, may quite suddenly develop malignant hypertension and the entire course be accelerated.

General Treatment

It should be emphasized at the outset that correcting the hypertension, even if that were possible, would not constitute cure of the disease. The hypertension is but one manifestation, though a very important one, of some underlying disease process. The nature and the cause of this process still elude us. Discovering the cause of the hypertension and removing that cause would be the way to help these patients. That ideal therapy is not yet here and until it is we must temporize with methods that leave much to be desired but which, nevertheless, can accomplish something in most cases and much in a few.

In that group of patients to which I referred before, who are fortunate enough to be free of symptoms and whose arterial tension is not very high, no active treatment is indicated. In general I should say that in these patients, especially if they are over 50, one need not attempt the more active methods of reducing the tension, and one should be content to institute a routine of somewhat lessened activity and more rest. Such a regimen should include rest periods each day, after luncheon or before dinner, ten hours of bed rest at night, warm baths for relaxation, a somewhat curtailed business day and vacations as often as the economic situation permits. Alcohol, coffee, tobacco may be used in moderation except by those who are specifically sensitive to

them. The diet need be altered only if the patient is obese, in which case a low calorie diet resulting in loss of weight may also result in a significant reduction in the level of arterial pressure. If the patient is apprehensive, and he is very likely to be, he will need reassurance and much explanation about the probable benign nature of his particular kind of hypertension. It seems wiser never to tell the patient the exact level of his tension or else he will be happy one day when it has gone down some insignificant degree and gloomy and depressed if it has gone up a comparable degree. Not telling the patient is better than deceiving him about the level, for sooner or later he is likely to find you out and his confidence in your integrity will be gone. These patients should not be seen too frequently lest they develop a feeling of invalidism, but they should be seen often enough so that the condition of the heart, vessels, kidneys and eye grounds may be checked. About four times a year would seem to be sufficient for that purpose.

The problem of what to do becomes more difficult in dealing with the group of patients whose tensions are higher and who are suffering from symptoms arising from the disease. To lower the tension, as I said before, is in no sense a cure of the disease; nevertheless, all the pathological changes which occur in this disease can be explained as resulting from the mechanical effects of a persistently elevated arterial tension. Therefore, even though the hypertension is not the primary cause of the disease but only a symptom, it is a symptom which dominates the entire clinical picture and which in its own right can cause all the disabilities which are known to occur in it. Above all, it is the hypertension which is responsible for the cardiac failure and for the arterial lesions which lead to the terminal event in over 75 per cent of all cases. It would seem therefore to be of the greatest advantage to the patient if the arterial tension were lowered.

For the purpose of reducing the tension innumerable remedies have been suggested. Up to the present time no really satisfactory method is available. But if we bear in mind the limitation of each method and the indications of each we can accomplish a great deal for a few selected patients. The routine which I suggest is this: When a patient who has been free of symptoms begins to develop headache, vertigo, irritability, insomnia (which symptoms are referable to the nervous system) or excessive fatigue, dyspnea, precordial pain (which symptoms are referable to the cardiovascular system) he should be given the benefit of

complete bed rest for a period of two to four weeks. The rest should be made as complete as possible and so far as possible he should be spared the usual anxieties and cares that are the lot of most of us. If headache is troublesome the head of the bed should be elevated 12-18 inches.

During this period, if the patient is obese, one may try the effect of weight reduction by a low calorie diet.

This enforced rest in a patient who is ordinarily vigorous and active may occasion restlessness and irritability and it is therefore advisable to use sedatives freely. Phenobarbital or chloral hydrate are the best. Bromide, which tends to be cumulative, is much less innocuous than generally believed.

The patient should be made to understand that the rest cure is of value whether or not the tension is lowered. And the doctor, too, should realize that benefit accrues to these patients by the protective action of rest on the cardiovascular system and the sedative effect on the nervous system, even if there is only an insignificant drop in the tension. In most patients, even though the drop in the tension is considerable, a resumption of their usual activities brings with it the return of the original level of tension.

Among the many drugs that have been suggested for lowering the tension, the only one that deserves serious consideration is *potassium thiocyanate*. This drug was introduced by Pauli in 1903 but the large doses recommended caused such disagreeable symptoms that the drug soon fell into disuse. Its use was revived by Westphal in 1924 and since then each year has witnessed reports on its use, most of which suggest that the drug may prove helpful. And yet the drug has never attained the acceptance which one would expect in the treatment of a disease as common as hypertension and with so little else to compete with it.

In 1932 Goldring and Chassis reported on their trial of the drug and concluded that, because of the uncertainty regarding proper dosage and the fact that frequently there is slight if any difference between the amounts that produce therapeutic and toxic effect, there is no place for it in the rational treatment of hypertension.

Following this report and largely because of their attitude the use of thiocyanate was generally abandoned. But in 1936 Barker reported that he had treated 45 patients with hypertension by sodium or potassium thiocyanate and had cotrolled the dosage by determinations of

the blood cyanate. He claimed that the reduction in the blood pressure and the relief of symptoms obtained in 35 of the 45 roughly corresponded to the level of the cyanates in the blood. He found the optimum therapeutic level between 8 and 12 mg. per hundred cc. and that toxicity begins to appear at from 15-30 mg. The method suggested for the determination of the blood cyanate is simple and takes less than 10 minutes to perform.

Following this report there was a renewed interest in the drug and numerous reports have appeared with conflicting conclusions:

Recently Goldring reporting further on his experience with the drug stated that thiocyanate should not be administered in hypertension because, apart from its toxic effects, its influence is not striking in either the frequency or extent of blood pressure reduction and that almost any medical or psychotherapeutic measure may be expected to yield results equally effective and with no element of danger.

On the other hand, we have the published opinion of Irvine Page who is an investigator of comparable experience who states that "There is no doubt that since Barker's introduction of the control of thiocyanate dosage by estimation of the thiocyanate content of the patient's blood, this drug has assumed a place of importance in the treatment of arterial hypertension."

The positions taken by these two important investigators in this field are absolutely opposite and seem entirely irreconcilable. It leaves the practitioner who is seeking some guidance in a quandary. Yet, if the published data of these two be carefully examined, it will be seen that their findings are not very different and that only their judgments are conflicting.

Goldring has considered the drug effective only if the pressure fell to 165 systolic and 100 diastolic; but in some of his cases there were marked falls in both systolic and diastolic pressure, yet, because the drop was not to the level arbitrarily set, the drug was declared ineffective. In spite of this Goldring and Chassis found that the pressure was effectively lowered in 31 per cent of the cases studied. They showed also that the hypotensive effect persisted from 7 to 110 days after the discontinuance of the drug. Almost invariably a fall in blood pressure was accompanied by subjective improvement.

The most disconcerting fact brought out by Goldring and Chassis was the frequency of toxic manifestations (13 out of 50 patients) and

the fact that two of these patients died. Barker maintained that such fatalities may be avoided by controlling the dosage by estimation of the level in the blood and the experience of others seems to bear this out. The fact remains, though, that occasional patients become toxic with a level of only 6 or 7 mg. per cent, while others tolerate a level of 20 mg. without untoward symptoms. The level which has seemed most likely to be effective without giving rise to toxic symptoms is the range between 8 and 12 mg. But in any case the optimal level must be carefully sought by gradually increasing the dosage to the point of effectiveness and lowering the dosage with any evidence of toxicity or sharp rise of the thiocyanate in the blood.

The toxic symptoms which should be carefully watched for are weakness, persistent bitter taste, anorexia, nausea, itching, dermatitis, purpura, mental confusion and disorientation. Evidence of toxicity is not likely to occur unless the concentration of the drug in the blood exceeds 15 mg. It is most likely to occur in older patients who have had severe hypertension for many years and in whom renal function is poor.

The patients most likely to be benefited are those under 60 who have shown no evidence of congestive heart failure, renal failure or cerebral change. Whether or not the anginal syndrome should be regarded as a contraindication is not clear but the probability is that lowering the blood pressure in these patients may increase the number and severity of their attacks.

Various methods of giving the drug have been proposed. The method I use is to give a 3 grain enteric coated tablet morning and night. If at the end of one week the tension has not been significantly lowered I increase the dosage to 3 such tablets. When the symptoms have been relieved and the tension lowered to about 160 systolic, 100 diastolic, an attempt is made to maintain this improvement by a daily dose of 3-6 grains. If after six to eight weeks of trial no benefit is obtained, the use of the drug is discontinued.

The thiocyanate level in the blood is determined once each week, using the method proposed by Barker. We have found this adequate for office practice even though it is difficult to make an exact reading. In hospital practice we use an accurate standard and make the determination with a photoelectric colorimeter. We try to keep the level between 8 and 12 mg. A level of 15 mg. should never be exceeded although many patients tolerate 20 mg. without untoward effect.

One might sum up the essential facts about the use of thiocyanate in hypertension by saying that: (1) it is the only drug which we have that in a considerable number of cases (one third to one half) causes a drop in tension which is of more than transient duration; (2) in about an equal number of patients it gives relief of distressing symptoms; (3) it may often cause toxic symptoms of minor character and rarely (6 reported cases) death; (4) it requires careful, close observation and skill in adjusting the dosage for each patient and determining a maintainance level which is effective but not toxic; (5) the determination of the drug level in the blood has been invaluable in controlling the dosage and preventing severe toxic reactions.

It is far from an ideal drug but when I am confronted with a patient whose tension is tending toward 250 or more I find it difficult to stand by and not use this drug since there is nothing else that is equally effective.

Surgical Treatment

Having done everything that medical treatment has to offer (having tried rest, sedation, psychotherapy, thiocyanates, etc.) sooner or later in a few cases when the disease shows signs of rapid progression and complete refractoriness to any therapy, the question of surgical intervention will arise. The public is now asking for authoritative information about it. It is up to the practitioner to familiarize himself with the new developments in this field, for it is he who finally decides which patients should be considered for this type of treatment.

The various surgical procedures that have been proposed are based upon the supposed relationship between hypertension and the adrenal gland, the sympathetic nervous system and the peripheral vascular system. The operations are of two general types: (1) The one type is directed at decreasing the secretion of the adrenal glands by resection or denervation; (2) the other attempts to paralyze the vasomotor control over large vascular areas.

Adrenal Gland: Two operations have been proposed based upon the concept that hypertension results from a hyperfunction of the adrenal gland: (a) Total denervation of the gland was done for the most part by Crile and failed to give satisfactory results; (b) the other procedure done on the adrenal gland was subtotal resection. The rationale of this procedure was similar to that in the treatment of exo-

phthalmic goiter. It was assumed that if the subtotal removal of the thyroid gland improved hyperthyroidism through the reduction of thyroid secretion, the subtotal removal of the adrenal gland should, by the reduction of adrenalin secretion improve hypertension. The operation has consisted in the partial removal of one gland, the total removal of one gland or the subtotal removal of both glands. While some reports in the literature are favorable, on the whole the results have been unsatisfactory.

To summarize the relationship between the adrenal gland and essential hypertension it may be said that there is no conclusive evidence either clinically, with patients, or experimentally, with animals, that shows a causal relationship; and that the surgical treatment based on this concept is for the most part unsatisfactory.

The possibility that chronic spasm of the splanchnic arterioles (by whatever mechanism this may be mediated) may be the basis of essential hypertension has been the basis for several operative procedures upon the sympathetic nervous system. There is evidence that suggests that the splanchnic vessels constitute an important flexible reservoir which governs the level of arterial pressure and that in essential hypertension the elevated blood pressure is due in part to constriction or loss of elasticity of the splanchnic vessels. Interruption of what is believed to be the chief vasoconstrictor nerve supply may then cause a reduction of arterial blood pressure. Based upon this idea are several operations which are intended to interrupt the sympathetic control of the splanchnic vessels. These operations include the resection of the splanchnic nerves above or below the diaphragm combined with removal of the lower dorsal or upper lumbar sympathetic ganglia; the removal of the celiac ganglia; and the division of the anterior nerve roots of a defined region of the spinal cord.

Three types of operations have been used: The supradiaphragmatic, the infradiaphragmatic and the transdiaphragmatic.

Supradiaphragmatic operation: Peet reported on 350 consecutive cases operated upon by him from 1933-1940: operative mortality, 3.4 per cent; 86.6 per cent had postoperative relief of major symptoms, especially headaches; 81.3 per cent had improvement or complete relief of incapacitation; 51.4 per cent had significant reduction in blood pressure. Approximately one-half of these patients had pressures reduced to normal or markedly reduced. Improvement in the ophthalmologic,

cardiac and renal status following operation varied from 45-70 per cent of the cases studied. Prognosis was better in females than in males. The most favorable results are obtained in the age group below 30. After this period the age seems of minor importance.

The infradiaphragmatic operation has been employed chiefly at the Mayo Clinic. The operative mortality is no higher than with the supradiaphragmatic operation. Allen and Adson have made the most important study of its effects in a group of 224 patients; 13 per cent are classified as good results, as judged by prolonged reduction in blood pressure, 18 per cent as fair, 39 per cent as temporary and 30 per cent as poor. All the group 4 hypertensives (malignant syndrome) did poorly. Although arterial pressure returned to its preoperative level in most patients, still many of them remained free of symptoms, especially headache, dizziness, fatigue, thoracic pain and shortness of breath.

The transdiaphragmatic operation was devised by Smithwick of Boston who has reported the results as follows: 58 patients were operated upon with 2 deaths following the first stage of operation. The results are derived from the study of 26 of these patients who had been studied from four months to two years. Six out of 8 group 1 hypertensives showed a significant change (by significant is meant a fall in arterial pressure to below 140/100 or systolic or diastolic was normal), 5 out of 5 in group 2, 2 out of 6 in group 3 and 4 out of 7 in group 4 (malignant). Smithwick has had a large experience with other types of sympathectomy and is in a position to evaluate with authority the results of operation. It is, therefore, of importance that he considers the results of the newer technique clearly superior to the older ones.

These operations on the sympathetic nervous system were designed to accomplish the following: (1) Denervation of a large vascular area, approximately the entire area below the diaphragm, and the denervation of the vessels carrying blood to the kidneys in order to eliminate the effects of vasospasm on the circulation in the denervated region; (2) to create a reservoir in the denervated vascular area when the undenervated vessels went into spasm; (3) the thorough denervation of the adrenal glands, by interrupting the sympathetic fibers before they entered the capsules of the glands (this should eliminate the central influence in producing excessive secretion and the flooding of epinephrine under emotional stress); (4) the thorough denervation of

the arteries which supply the kidneys should increase the circulation of the kidneys and might aid in elimination of metabolic products which if present and retained might produce pressor effects on the arterial tone.

The selection of patients for operation is probably as important in determining the end results as the actual operative procedure. For the most part operation should be reserved for patients whose hypertension, if mild, is definitely progressive in spite of medical supervision, and for those who have severe hypertension which has not responded to medical treatment.

There are no infallible criteria for selecting patients at the present time. However, the patients whose blood pressures decrease to normal or nearly to normal as results of rest or sleep, or oral administration of 3 grains of sodium amytal every hour for 3 successive hours, or the slow, intermittent intravenous injection of a 5 per cent solution of pentothal sodium to produce light anesthesia, receive the greatest benefit from operation. A satisfactory response to these tests indicates that the arterioles offer increased resistance to the flow of blood largely by virtue of functional, hence reversible, changes and not as a result of organic, hence largely irreversible, changes. Conversely, those patients whose blood pressures do not decrease satisfactorily as a result of these measures, benefit from operation, as a group, to a substantially less degree than do those whose pressures are still labile. One need not consider as contraindication to operation sclerosis of the retinal arteries, moderate enlargement of the heart, inversion of the T waves in EKGs, albuminuria, slight reduction in renal function or cerebral vascular accident from which recovery has been satisfactory. However, it is not advisable to operate on patients who have congestive heart failure. marked renal insufficiency, advanced arteriosclerosis, or angina pectoris. Perhaps as experience increases, even some of these patients may be considered suitable for operation. About 80 per cent of cases were benefited. Blood pressure in 45 per cent was not reduced.

To summarize the status of the surgical treatment of hypertension one would be justified in saying that lowering of the blood pressure has been shown to follow in a significant number of cases but that it has not been shown to be permanent in all; that improvement in the subjective and in some of the objective manifestations of the disease has been even more frequent. This has been especially true of the headaches.

in which a striking improvement is usually noted. In some cases improvement in the eye grounds has been noted, with disappearance of papilledema, hemorrhage and exudates. Which of the operative procedures will eventually be shown to be most effective cannot now be foretold; but the trend seems to be toward the more extensive operations such as the Smithwick.

Renal Extracts

A number of investigators have claimed favorable results from the administration of renal extract. The rationale for its use has been summarized by Grollman, Williams and Harrison as follows:

1. Tigerstedt and Bergman showed that renin induced a greater rise in blood pressure in nephrectomized than in normal animals. They attributed this difference to failure of the nephrectomized animals to excrete the pressor substance. In repeating their experiments Merril, Williams and Harrison noted that the increase in sensitivity did not appear immediately after nephrectomy but only after a number of hours had elapsed. This led them to suspect that normal renal tissue might form some substance which was distributed in the body and which had the property of limiting the pressor effect of renin.

2. Further indirect evidence for the existence of a renal antipressor substance was furnished by the experiments of Blalock and Levy, who showed that in an animal with unilateral ischemia, removal of the normal kidney resulted in a marked rise in blood pressure.

3. Additional support for the existence of an antipressor substance was furnished by experiments in which it was shown that extracts of normal kidneys tended, on standing, to lose their pressor property more rapidly than did similarly prepared extracts of ischemic kidney of the same animal.

4. Another piece of indirect evidence for the existence of a humoral antipressor substance is the observation that hypertensive pregnant animals commonly develop a well marked decline in blood pressure during the last part of pregnancy and that the blood pressure increases to its previously elevated level following delivery. It would be difficult to account for such a sequence of events except by assuming that the fetus or the placenta forms some substance capable of reducing the elevated blood pressure of the mother.

The observations which have been cited all suggest that the kidneys

elaborate some substance which has the property of inhibiting the pressor effect of certain agents, including the renal pressor substance renin. Direct evidence of the validity of this hypothesis was obtained when it was found that extracts prepared from the kidneys of various animals did diminish the sensitivity of rats to renin and certain other pressor substances.

Extracts containing this antipressor substance were then administered to animals with experimental hypertension by Grollman, Williams and Harrison. They found that there was in these animals a decline in blood pressure. These same investigators then administered the extract orally and parenterally to a small number of patients with hypertension. In most of the subjects a decline in blood pressure occurred. However, they have refused to draw any conclusions as to the therapeutic effect in patients. They feel that the drop in blood pressure may be spontaneous, though this is unlikely; and that the subjective improvement may be due to suggestion.

Page and his co-workers have reported results in animals and patients which are essentially the same.

On the Third Division at Bellevue Hospital Goldring and Chassis have been testing renal extracts on two cases of essential hypertension and on two cases of hypertension due to chronic glomerulonephritis. The daily dose has been the amount of extract obtained from 50 kilograms of beef kidney. This has been given by mouth for several months. There has been no significant fall in the arterial pressure in any of them.

To summarize the present status of therapy by renal extracts, one might say that, though experimentally in animals they have shown some degree of effectiveness, in many they have been entirely ineffective when given by mouth. When given intravenously they have been effective in lowering the arterial tension but only when the treatment has been associated with a general systemic reaction usually with fever. This type of reaction is not specific for renal extracts, and similar effects may be obtained by the intravenous injection of any foreign protein such as typhoid vaccine. From the standpoint of the clinician the renal extracts have nothing to offer at this time.

Amine Oxidase

Another medical treatment is based on the theory that ischemic renal tissue, being deprived of adequate oxygen, fails to deaminize the

amines and since the amines are pressor substances, their accumulation in the blood results in hypertension. It has been suggested, therefore, that amine oxidase be given to correct this. Tyrosinase has been tried by some and quinones by others. In experimental hypertension in animals the effects have been striking but the evaluation is subject to the same difficulty as with renal extracts in that the pyrogenic reaction, occasioned by the treatment in itself, could account for the lowering of pressure. From the clinical standpoint this method has no value.

Psychotherapy

Finally, a word about psychotherapy in these patients. Those who have been stressing the psychosomatic aspect of the disease believe that in some cases the hypertension arises because of suppressed aggression or rage. I have spoken to several psychoanalysts who tell of cures accomplished when such a neurotic mechanism was removed. Whether this is true or not, I do not know but no one can doubt the value of some form of simple psychotherapy. Much can be accomplished by a friendly understanding and encouraging chat in which the physician explains the natural history of the disease, stressing its long course, directing the attention away from the blood pressure and even pointing out that it may be better not to lower it.

If any one doubts the value of psychotherapy, let him recall how often patients feeling well have consulted him, been told that the blood pressure had gone up a few points and then had left the office low in spirits, weakened and depressed. Conversely, how often do these patients, being told that their blood pressure had dropped, become elated and relieved of many of their symptoms. We must maintain for the benefit of these patients an optimism which alas! we often do not feel but which, even if simulated, may be used as an effective therapeutic measure.

Summary and Conclusion

1. All cases of hypertension should be studied to rule out primary renal disease.

2. This is especially important because of the possibility that the primary renal disease may be unilateral and amenable to surgery.

3. In cases of essential hypertension one should bear in mind that the disease may be latent at birth and develop gradually over several

decades; hence the importance of studying each case in order to obtain a more accurate orientation and a better judgment of the outlook.

4. In most cases it is not necessary to try to reduce the arterial tension and it is not even clear that this is always an unmixed good.

5. Thiocyanate is the only medication that in any considerable percentage of cases lowers the arterial tension.

6. The cases in which surgery is indicated are few and the benefits still problematical but this form of therapy is receiving increasing attention.

7. Treatment by renal extracts and by amine oxidase has a reasonable background but practically these methods have been unimpressive.

8. Psychotherapy has a place in the treatment of every case of hypertension. Whether or not it is useful in removing some neurotic mechanism that may be related to the development of hypertension, it can always help the patient adjust to the limitations imposed by the disease.

SEQUELAE AND COMPLICATIONS OF CONVULSIVE SHOCK THERAPY*

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IN THE evaluation of a therapeutic measure we balance the therapeutic efficacy and urgency of the treatment with the potential risks and health hazards of such treatment. In view of the increasing popularity and widespread use of convulsive shock treatment for various psychiatric disorders it would seem justified that we consider in some detail any undesirable or untoward effects resulting from these treatments. Our information relative to such effects is drawn largely from observations and follow-up studies carried out on about 300 patients and also to a substantial degree from the experiences and reports of other investigators.

Of course, the most serious complication is death. This is only rarely encountered and in fact in well selected and well prepared cases is never encountered. Thus far there have been no mortalities directly attributable to the treatment in over 500 patients treated at the Psychiatric Institute.

Kolb and Vogel,[1] in an analysis of figures from several hundred institutions in the country listed only four deaths as attributable to electroshock treatment in 7,207 cases, a death rate of 0.5 per thousand. This compares with a death rate of one per thousand in metrazol-treated cases and 6 per thousand in insulin-treated material. In an analysis of fatalities throughout the United States, up to June 1942, Doctors Ebaugh, Barnacle and Neubuerger[2] found ten deaths, two of them occurring in their own experience. However, some of these deaths apparently were not directly or immediately the effect of the induced convulsion since the condition responsible for the exitus occurred some months after treatment. More recently Impastato and Almansi,[3] in a review of the literature, reported 8 electric shock deaths in an estimated 11,000 cases. It is important to note that in 4 of these

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cases death was attributable to cardiac complications; the others died of pneumonia, pulmonary edema and post-convulsive respiratory arrest, while in one case the cause was not definitely ascertained.

Although one obtains the impression that cardiovascular involvement precludes the use of convulsive therapy it has been our experience and the experience of many others that individuals with varying degrees of cardiovascular disease, with or without abnormalities in the electrocardiogram, ordinarily tolerate convulsions well, providing the disease is not too acute or severe. Most cardiovascular disturbances occurring after electroshock are transitory, usually disappearing within 5 to 30 minutes and generally consisting of bradycardia, extra-systoles and sinus arrhythmia. In a few instances cardiac collapse occurred immediately after the convulsion with the patient exhibiting marked pallor, weak, slow and irregular pulse and low blood pressure. These cases recovered spontaneously after each treatment. Although it has not occurred in our experience, cardiovascular reactions have been reported where apparently cardiac failure appeared some time after electroshock, perhaps 20 or 30 minutes later and subsequently cleared up. Some investigators have reported complications in patients with valvular disease. Ziegler[4] mentions a case of old endocarditis which flared up after convulsive therapy, while another case with rheumatic chronic valvular disease reported by Kline and Fetterman[5] showed temporary cardiac failure about 20 minutes after the first convulsion and recovered in about 30 minutes subsequently. The cardiac deaths earlier referred to have been caused by dilatation of the heart, myocardial damage, ventricular fibrillation and coronary occlusion. Evans[6] has reported the use of electroconvulsive therapy in patients with coronary disease, auricular fibrillation and hypertension with no ill effects on the course of the heart disease.

We have routinely employed electrocardiograms prior to shock treatment and have been exceedingly cautious in proceeding with the treatment where the EKG shows substantial cardiac disturbance, where there has been a history of rheumatic heart disease with clinical signs of vascular damage, or a history of previous coronary disturbance. Some believe, however, that a cardiac decompensation is the only absolute contra-indication to shock therapy.

A number of interesting observations relating to blood pressure changes have been recorded in connection with shock therapy.

Menninger[7] reported the case of a patient who developed hypertension during a course of metrazol shock treatments and which persisted over four years afterwards, although the patient had had a normal pressure prior to treatment. I might mention that two of our own cases, one of whom received metrazol and the other electric shock therapy also exhibited a hypertension varying from 160 to 180 mm. of pressure systolic, some months after therapy. One of the patients was a 40 year old agitated depression who showed complete remission of psychiatric symptoms with treatment, even after a period of 3 years. The other patient was diagnosed as a catatonic schizophrenic who showed excitement features during the illness and became much improved subsequent to treatment. Both patients had normal tensions prior to treatment. It should be noted, however, that the blood pressures were not routinely taken in all patients after shock therapy, but were taken in only a relatively small number of cases and in a few who complained of dizziness or headaches as these two patients did. We, therefore, do not know whether more patients developed an increased pressure. On the other hand we have no control group of psychiatric patients of a similar type who received no shock therapy and who were subsequently studied for tension changes so that it is quite possible that the increased pressure in the two cases might have occurred whether shock therapy was given or not. It is known that the blood pressure becomes elevated during and for a short period immediately after a seizure but then soon drops back to the pre-seizure level, or to an even lower pressure than prevailed before the treatment. Very often patients with increased pressures prior to therapy, in some instances exceeding 200 systolic, exhibited a substantial lowering of the tension as their clinical condition improved; it is probable that this is more frequently the case rather than an elevation of blood pressure after therapy.

There is some question regarding the possibility of rupture of vessels during the seizure. Although subconjunctival hemorrhages are occasionally noted, retinal hemorrhages have not been observed. We have had no occasion to suspect the presence of intracranial hemorrhage. Studies of spinal fluids immediately after a convulsion in metrazol-treated patients revealed no evidence of subarachnoid bleeding. We might mention the case of Ziegler[4] where the patient had a subarachnoid hemorrhage 2-3 years prior to treatment and showed no untoward effects with shock therapy.

With respect to pulmonary and respiratory complications, the most frequent and consistent occurrence is apnea, which is present during the actual convulsion and which persists for short varying periods after the seizure, generally not exceeding 30 seconds. As mentioned above, there has been only one case reported in the literature of respiratory arrest which resulted in death. Ordinarily, a few applied artificial respirations are sufficient to bring on spontaneous respiratory movements in a prolonged period of apnea.

Occasionally one observes a post-convulsive stridor which might be caused by nasal obstruction and blockage of the air passage through the mouth by means of the gag. This is readily cleared by manipulating the gag so as to secure an air passage through the mouth. On frequent occasions, we have found that the stridor can be relieved by applying firm pressure to the jaw upwards and slightly retracting the head.

We have experienced only one instance of pneumonia which occurred within 36 hours after the patient received a convulsion. This patient cleared up with the use of sulfadiazine in a few days and after a two-week interval, convulsive therapy was reinstituted. After three treatments she again developed a pneumonic consolidation in the opposite lung, which again cleared up rapidly with sulfadiazine. There have been reported in the literature instances of pneumonia occurring in association with insulin shock therapy, but this is a rare occurrence in convulsive shock. With the exception of one case of lung abscess reported by Kalinowsky,[8] no other such complication has been mentioned in the literature. We have encountered no such cases in our own material. It may be noted that abscesses are not too uncommonly observed in insulin treated patients.

We might mention that in a few instances where patients had mild upper respiratory infections without elevation of temperature, we have observed no untoward effects with the administration of shock, although we generally prefer to postpone treatment in these instances.

The question as to whether convulsive treatments activate or aggravate tuberculous lesions is not yet fully decided. A number of studies have been reported for metrazol-treated cases,[9, 10, 11] where tuberculosis is reported to have been activated and also where there was an indication of an increased incidence of tuberculosis in the treated material. We are not aware, however, that any of our own patients have shown any reactivation of tuberculous lesions. At least four of our group gave

histories of active tuberculosis at some time within a 15-year period prior to shock therapy, which required prolonged medical care and bed rest in order to effect healing of lesions. None of these patients showed a reactivation of tuberculosis. An additional patient whom we treated had a therapeutic pneumothorax at the time of treatment but she went through the course of shock therapy without ill effects and subsequently showed improvement in her pulmonary condition concomitant with the improvement in her psychological status. Smith[12] administered convulsive therapy to an agitated, middle-aged female who at the time of the treatment exhibited active tuberculous lesions of several years duration in both lungs. There was about 200 cc. of fluid in the left pleural sac and pneumonic consolidation in the right lung. She was running a daily elevation of temperature of about 1-2 degrees. However, this patient showed no untoward effects in a series of 20 electro-treatments. She improved both in her psychiatric status and in her pulmonary condition. However, we cannot negate the possibility that in these cases complications might occur with shock treatment, and that it is necessary that we judge each individual case on its own merits and balance the severity of the psychiatric symptoms with the severity of the pulmonary tuberculosis.

We have not noted any serious or severe gastro-intestinal complications in our material, although Ziegler[4] reports a patient with gastric ulcer which bled after a convulsion. Post-treatment nausea is quite frequent, but generally disappears within a half-hour after shock. Vomiting rarely occurs. Biting of the tongue and lips may sometimes occur, although with ordinary care and precaution in the handling of the mouth gag, this can be prevented. It is advisable, incidentally, that all easily removable dentures be taken out of the mouth before each shock treatment.

Complaints referable to the muscles are quite frequent, but not serious. After the first convulsion the individual usually complains of cramps or soreness in the muscles of the limbs and back. Very often the soreness is most marked close to or between the angles of the scapulae, but no local tenderness is present as a rule unless there are other complicating features such as vertebral fracture or tearing of the muscle. The latter is only rarely encountered. Savitsky[13] mentioned a tear in the deltoid muscle which healed uneventfully. The myalgias are observed more frequently in well-built muscular individuals than in other types

of persons. It is not too uncommon for patients to complain of an achy feeling in the muscles of the chest on inspiration, after a course of shock treatments. This usually subsides very soon after the treatments, although in a few instances this feeling persisted for some months after therapy and then disappeared.

The skeletal system is commonly involved in complications, with vertebral compression fractures a relatively frequent occurrence. The region usually involved is the midthoracic spine. The fractures vary in severity, at times being quite marked but in the majority of instances being only mild in degree. It appears that maintaining hyperextension during the treatment reduces the incidence of such fractures. Statistics regarding the incidence of vertebral fractures vary widely. Impastato and Almansi[3] in examining the literature found that there were 39 cases of fracture of the thoracic spine reported out of a total of 1750 cases, or an incidence of 2 per cent. Polatin et al[14] had previously reported an incidence of approximately 43 per cent in metrazol-treated cases with extension and Horwitz,[15] in a study of electric shock cases where hyperextension was employed found approximately 20 per cent fractures. It is to be noted, however, that in the studies by Polatin and by Horwitz which were conducted at the Psychiatric Institute, the patients were x-rayed routinely after termination of treatment. It is our impression that this was not done in the material reviewed by Impastato, where it is more likely that only those cases were x-rayed which showed suggestive symptoms of possible fracture. It has been a frequent experience in routinely x-raying patients after the end of therapy, that many cases of fracture are observed where the patients have no symptoms at all. Even in the severe compression fractures, where 2 or 3 vertebrae may be involved, symptoms are surprisingly mild and do not generally persist for more than several days after the last treatment. In a few instances, however, back pain and local tenderness on deep pressure have continued for several weeks. In 2 cases where back pain persisted for some months the patient exhibited no fractures and it was believed that the symptoms might have been related to some tearing of muscle or of other soft tissue structures. It has been the general observation that these fractures heal well even when multiple, without splints or immobilization and without any residual or subsequent neurologic or physical findings. If fractures of the vertebrae occur early in the course of treatment, the question always arises as to whether the shocks should

be continued. This depends, we should say, to a large extent upon the severity of the psychiatric picture and the extent of the injury. If the injury has not been too severe and psychiatric symptoms are expected to show good remission with further treatment, it has been our custom to go ahead with treatment. One could perhaps employ curare in such instances to lessen the severity of the contractions.

We have encountered one instance of fracture of the neck of the femur. Similar fractures involving not only the femur but also the other long bones and also the hip bones, clavicles and scapulae have been reported. These are very rare complications and perhaps can be prevented if the patient is not permitted to swing about wildly during the convulsion. However, when one of these fractures does occur, they are generally more troublesome and difficult to handle than are the fractures of the spine. Since they are more prone to occur in elderly people, the fracture is likely to be a rather disabling one.

Curare has been utilized for softening the severity of contraction of the muscles during the seizure in an attempt to diminish or eliminate the incidence of fractures. Some have advocated the extreme point of view that this drug be used as a routine procedure in combination with convulsive therapy. Bennett[16] has advocated this viewpoint, and has reported a marked diminution or absence of fractures in the curarized patients. Cash and Hoekstra[17] administered 995 combined curare-electroshock treatments to 139 patients and reported no traumatic complications in this group, but reported one death. We might mention the observation of Impastato and Almansi[3] that 50 per cent of the 8 electric shock cases so far reported in the literature to have died as a result of electric convulsive therapy received curare prior to treatment. This may be significant when we regard the relatively few individuals who have been treated by preliminary curarization in electric convulsive treatments. We have hesitated to use this drug routinely in combination with electric shock and have the impression that the danger attendant with the routine administration of curare plus the undesirable psychological effects it seems to have in many patients is not sufficiently compensated for by its minimizing effect on the severity of the muscular contractions and the resulting diminution of fracture incidence.

Dislocations of the jaw sometimes occur but they are easily reducible immediately after the convulsion. These dislocations usually can be prevented by holding the jaw firmly upward at the time the shock

is administered and also during the seizure. Most frequently the jaw is dislocated at the onset of the seizure when the mouth is suddenly and widely opened and the mandible is thrust forward.

There have been very few objective or even subjective neurological manifestations as complicating features of convulsive therapy and none of these have been of a very serious or incapacitating nature when the individuals have been clinically normal prior to treatment. Occasionally patients may complain of numbness and tingling sensations in the limbs but this disappears within several days as a rule. In a few instances patients have complained of tinnitus and buzzing in the ears for several days following treatment. One patient who showed complete remission complained of continuous buzzing for about 2 weeks. Three patients have complained of attacks of dizziness, in one instance accompanied by fainting spells. These attacks would come on suddenly at any time of the day, and almost simulate a Ménière's syndrome. One of these patients, who received metrazol about three years ago, exhibited congenital nystagmoid movements prior to treatment. A second patient showed signs of cerebral arteriosclerosis and complained of mild dizziness prior to therapy while the third patient was apparently suffering from a concussion syndrome in addition to her psychotic state. These latter two received electro-shock. The first and third cases have continued to show marked dizziness while the third exhibits in addition, fainting spells. The patient with arteriosclerosis has cleared up. It may be mentioned, incidentally, that in all three cases electroencephalograms had returned to normal after the treatments in spite of persistence of symptoms.

Of all the patients who received convulsive therapy two have developed spontaneous seizures. These occurred some weeks after the last treatment. Electroencephalograms had been taken prior to therapy, and in both instances revealed significant abnormal features. Electroencephalographic tracings taken after treatment continued to maintain marked abnormal features. It should be stressed that no patient with a normal electroencephalogram has developed any spontaneous convulsions. It appears that the two patients who developed post-treatment seizures and who, incidentally, presented no history of previous attacks, had latent convulsive tendencies as evidenced by the electroencephalograms. It is reasonable to assume that these tendencies were reinforced by shock treatment. We cannot subscribe whole-heartedly to the

opinions of some who believe that shock can be given with impunity to epileptics. This entire question is to be taken up in more detail in a separate report.

Spotnitz mentioned that metrazol-treated patients exhibited a persistent impairment of gustatory and olfactory perceptions. We have not been able to confirm this by gross clinical means nor have we noted anything in the literature regarding this, but it is possible that finer testing might bring out some impairment in these sensory spheres.

Other neurologic complications have been reported in the literature. Impastato[3] quotes Trampler and Reisner as having reported a case of aphasia; another of brachial plexus neuritis and another of acute parkinsonism, following electric shock treatment. However, the possibilities of such complications appear to be extremely remote.

The question as to whether actual histopathologic changes occur or persist in the brain is subject to controversy. Some have reported capillary hemorrhages, gliosis and neuronal changes in experimentally produced convulsions in animals,[18-21] while others have denied these findings.[22, 23] We have studied a series of monkeys who received a "course of electrical shock treatment" similar to that received by humans and have found no significant histopathologic alterations.[24] Of course one could always argue that a normal clinical status or at least a socially adaptable individual with a little brain pathology is preferable to a psychotic patient with no demonstrable brain changes.

Electroencephalographic tracings have been studied extensively in connection with convulsive shock.[25-29] The changes reported have been found to be largely reversible. However, in a few instances, particularly in those patients who received many treatments (exceeding 12 convulsions within the course of a month or six weeks), the electroencephalogram still showed abnormal features a year after treatment.[28] It should be emphasized, however, that the presence of abnormalities in the electroencephalogram is not necessarily equated with histopathologic changes in the brain which could necessarily be demonstrated by the usual techniques. It is problematic whether shock therapy should be administered in patients showing certain types of abnormal electroencephalograms. This matter has been investigated by us and will be presented in a separate communication.

Psychologic changes have been very frequently observed in patients subjected to shock treatments. The most striking complicating feature

is the memory defect. This is noted early in the course of treatment and with increasing number of treatments becomes more pronounced and more persisting. The memory defect is both retrograde and anterograde and is somewhat "lacunar" or spotty in type. It has been suggested by some that the patient forgets those things which he wants to forget or which have been the most sensitive or traumatic for him. We do not believe there is sufficient evidence for this opinion. As a rule, the memory defect disappears or markedly diminishes after a few weeks, but occasionally the patient still complains of slight memory loss for several months subsequent to treatment. In two instances the patients complained of memory impairment for as long as a year after therapy. However, the disturbance from the clinical point of view is relatively slight. A number of attempts to study this memory defect have been made by utilizing objective psychologic tests. Studies conducted by Zubin[30] of the Psychiatric Institute in which recall, relearning and recognition were tested, led him to believe that electric shock treatment does not in any way destroy memory, but simply disorganizes it. In other words, the memory traces are not lost, but are temporarily dissociated. He also concluded that the learning and retention process is only very temporarily affected since no ill-effects are noted in the post-treatment period. However, extensive testing of the memory over a prolonged period of time subsequent to shock was not carried out. It should be borne in mind that the control memory tests were given to psychiatrically ill patients and that the results were then compared with those obtained when the patients had received shock and were possibly in clinical remission of symptoms. In spite of this possible source of error, Zubin's results are very much in accord with our own clinical impressions.

There has been some question as to whether the intellectual level is affected but clinical observation of these patients over a period of time has given no gross evidence of actual intellectual deterioration which could be definitely ascribed to shock therapy. Nevertheless, there is certainly a need for more objective psychometric testing of these patients.

An evaluation of actual personality changes was made with the use of the Rorschach test. It is interesting that the patients exhibited an organic type of change of a diffuse type within the first hour subsequent to shock treatment, but after this the Rorschach analysis illustrates

the same personality features as were exhibited by the individual prior to the treatment even though he had no recollection of having been subjected to this procedure before shock. In this connection it should be stated that patients show varying degrees of confusion as a result of the shock treatments. This is usually mild, with the degree of confusion depending largely upon the frequency and number of the treatments, but varying considerably from patient to patient. The confused state is essentially an "organic" type reaction, in which the patient may become disoriented for time, place or person, and exhibit memory defect, particularly for recent events. It is generally more pronounced in elderly or arteriosclerotic patients, but usually disappears within 1 to 3 weeks after treatment, lingering on only in the form of the memory defect mentioned above.

In the course of convulsive therapy, it is often observed that the symptoms of the illness, particularly where depressive and anxiety features are prominent, may be temporarily exacerbated during the first few treatments. This seems to be due, at least in part, to the patient's reaction to the memory defect, causing an intensification of anxiety and motor restlessness, and necessitating constant reassurance by the physician. However, with further treatment the anxiety and depression diminish substantially, but at the same time the memory defect becomes more pronounced. The patient, however, is no longer especially concerned with the memory disturbance, although is still well aware of it. At this stage or towards the end of the treatment the patient may exhibit a mild hypomanic or euphoric state, which in some instances persists for some weeks before levelling off. In older individuals it is deemed advisable to exercise some restraint over the hypomanic drives of the patient, particularly if there is an associated hypertension. Very often, too, judgment during this phase might be impaired and a certain degree of caution must be emphasized to the patient or family.

One or two miscellaneous points might be mentioned. In occasional instances, a patient may complain of amenorrhea subsequent to shock treatment, even though there may have been complete regularity during and prior to the illness. We have not noted any permanent or long-continued cessation of menstruation, however. It might be of interest also to mention that 2 cases of pregnancy were given convulsive therapy, both of whom were in the fourth or fifth months of gestation. One of these patients was delivered of a normal healthy infant at full

term. We were unable to follow the course of events in the second patient, but up to the seventh month, the patient appeared to be getting along very well in her pregnancy, with no untoward effects.

Conclusion

It appears reasonable to conclude that the possible complications which are entailed by the use of convulsive therapy are far outweighed by the therapeutic benefits resulting from such treatment in the properly selected cases. Where a physical illness or defect is present to the extent that it offers a substantial risk for shock therapy, it becomes necessary to balance this potential risk against the severity of the psychiatric illness and the chances of therapeutic benefit which could result from the treatment.

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AMICROBIC PYURIA*

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In the last decade treatment of infections of the urinary tract has been fairly well standardized. Certain general principles of diagnosis and treatment have been laid down and are well known. To me, the most interesting part of the whole problem of urinary infections is its relative simplicity, for if the general physician and the urologist will approach the question of treatment with a few well-organized principles in mind, a large percentage of infections of the urinary tract may be cleared up early and completely before they have time to produce changes in the kidneys, ureters or bladder which materially complicate the problem.

It seems unnecessary to mention to a group of urologists that first of all, before treatment is undertaken, the presence of an infection of the urinary tract and the general site of the infection should be established. Each year my colleagues and I at the Mayo Clinic see a number of women patients who have been taking mandelic acid or one of the sulfonamides to the point of tolerance in an effort to eradicate an infection of the bladder and kidneys which actually does not exist. It is true that these patients have burning and frequent urination and pus in the urine. The administration of various chemotherapeutic agents, however, has produced little if any benefit. On questioning the patient it often is found that only voided specimens of urine were examined, and when a catheterized specimen is examined, it is entirely free of pus or organisms. In this group of cases the detailed examination and history suggest inflammation of the urethra, and cystoscopy frequently reveals chronic granular or cicatricial urethritis or both. Local treatment for a few days is usually of great benefit and the patient is relieved.

In men pyuria frequently can be proved to be of prostatic origin. Chemotherapy for this type of pyuria is of little value. Thus, when females have pyuria or other symptoms of urinary infection a specimen

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of catheterized urine must be examined and when males have these symptoms the two-glass test of urine should be done routinely before treatment is instituted in order to determine whether the infection may involve the kidneys, ureters, or bladder.

Having once established the presence of an infection of the kidneys, ureters or bladder, it is now of value to determine the type of organism producing the disease and the presence or absence of any primary or secondary contributing pathologic infection. By no means do I wish to infer that every patient suffering from an infection of the urinary tract should have a complete urologic examination, including urographic and cystoscopic studies. However, I do feel that because of the well-known efficacy of mandelic acid and the sulfonamides in eradicating uncomplicated infections of the kidneys, ureters and bladder the use of these drugs should not be continued indefinitely. If two courses of treatment do not bring about sterilization of the urine, then the patient is entitled to a complete urologic examination in order to ascertain the presence of any existing condition in the urinary tract, such as stone, stasis, tumor, and so forth, which is hindering the action of the drug.

The importance of the infecting organism has been clearly demonstrated, but a few words of repetition seem indicated. Simple Gram's staining of the urinary sediment should be done in every suspected case. Examination of slides after Gram's staining will divide the cases into two groups: the first, those with demonstrable organisms, and the second, those without demonstrable organisms. It will divide the first group further and indicate to the physician whether he is dealing with a bacillary or coccal infection and whether the organism is gram-positive or gram-negative.

It is the second and smaller group of cases without demonstrable organisms which I should like to discuss in detail in this paper, because I am certain that their existence is not fully appreciated by either the general physician or the urologist. All physicians were taught early in their training to consider sterile or amicrobic pyuria indicative of a tuberculous infection of the urinary tract. Undoubtedly, this is the usual cause but by no means does it account for all such cases. What then is the etiologic factor in these cases?[1-4] Is an ultramicroscopic organism or a filtrable virus the causative agent? Is bacterial invasion of the renal parenchyma present without any organism reaching the tubules and hence the urine? If such invasion occurs, are the cellular elements

in the urine the result of the inflammation produced by the liberated toxin? Another possibility is that the toxins liberated by foci of infection elsewhere in the body are excreted by the kidneys and produce the resulting inflammatory reaction. Ewert and Hoffman,[5] Moore,[6] and others in their writings suggest an ultramicroscopic organism or filtrable virus as the most likely cause of pyuria without demonstrable organisms. Studies at the Mayo Clinic certainly cannot disprove this hypothesis but I feel that in a large number of cases foci of infection elsewhere in the body contribute to the etiology of the inflammatory reaction in the urinary tract, and unless these foci are eradicated, complete cure is difficult to obtain.

The duration of the disease varies. Originally it was my impression that it was present for months or even years in most cases but as ability to recognize it increased a number of patients have been seen early in their illness. The local symptoms are referred to the bladder and urethra and are usually severe—more severe, indeed, than those seen in the usual bacillary or coccal infections of the urinary tract. Dysuria and frequent urination with tenesmus are the rule. Sometimes there is hematuria and on occasions the distress reaches the point of stranguria. Systemic reactions are not common but in a few cases pain in the loin with chills and fever, general malaise, anorexia, and so forth have been noted.

The urine is loaded with cellular elements; leukocytes, erythrocytes and epithelial debris. Repeated Gram's staining and staining of the urinary sediment for acid-fast bacilli and repeated cultural studies fail to reveal any infecting organisms. The finding of so-called sterile pyuria, of course, should bring to the examiner's mind the possibility of a tuberculous infection and this condition must be ruled out by repeated use of stains to indicate acid-fast bacilli and inoculations of guinea-pigs. A large number of the patients suffering from such pyuria not due to tuberculosis have been submitted to an intensive anti-tuberculosis regimen which entailed an entirely unnecessary economic burden. Because of the occasional difficulty in finding the tuberculous organisms in stained slides of urine and the length of time required to carry out the guinea-pig test, a tentative diagnosis of tuberculosis is made. However, failure to find certain clinical signs of tuberculosis of the urinary tract should tend to exclude this condition even before the laboratory reports are received. These signs, however, generally are not known. Bumpus and Thompson[3] have shown that in 80 per cent of

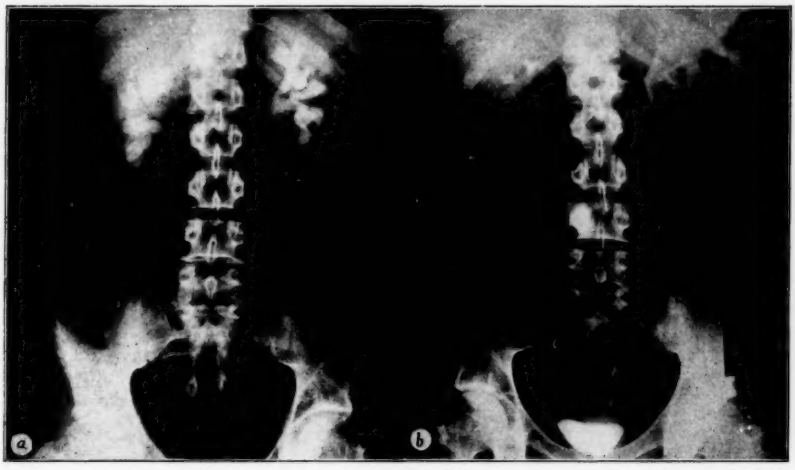

Fig. 1—Urograms in a case of amicrobic pyuria *a*, before treatment; dilatation of the renal pelvis and calices may be noted; *b*, after treatment.

the cases of tuberculosis of the upper part of the urinary tract the genitalia are involved also. In such cases the clinical findings are nodular and thickened epididymides, beaded pipestem vasa deferentia, or nodular prostate gland. The diagnosis of tuberculosis should never be made without corroborative evidence other than the apparently sterile pyuria and some suggestive cystoscopic or urographic findings.

Cystoscopic findings in cases in which non-tuberculous, sterile pyuria is present are a reduced vesical capacity, extreme irritability and diffuse involvement of the vesical mucosa with redness, edema and at times ulceration. These findings usually appear to be superficial, but in the cases of infection of long standing the deeper tissues seem involved as well. Ureteral catheterization almost always reveals bilateral renal infection of varying degree. One side may be involved to a greater degree than the other side. Renal function is rarely impaired except in the late stage of the disease.

Urography frequently discloses dilatation of the pelves, calices and ureters which is suggestive of an inflammatory origin, and in other cases the urographic findings are negative. Positive urographic findings may invite a certain pessimism with regard to prognosis but this should not be. Urograms made in the case of a young man (Fig. 1*a* and *b*) suffering from this type of infection of the urinary tract indicate the

change in conditions before and after treatment. The return to normal is frequently noticed if the disease is not too longstanding.

Experience during the last decade has taught a great deal regarding treatment of these conditions. Primarily it has been learned that the usual urinary antiseptics given by mouth are of little or no value. None of the sulfonamide compounds or mandelic acid is effective in relieving symptoms or reducing the pyuria. Local therapy if carried out intensively may be helpful but by no means is it as useful as in the infections with demonstrable organisms. In a few cases the infection is so severe that examination is required in the hospital, and continuous irrigating systems for vesical lavage must be employed. In these cases gradually increasing strengths of solutions of silver nitrate, beginning with a 1:10,000 solution and proceeding to a 1:1,000 solution, if possible, have been used with benefit. This type of lavage, however, is usually only a palliative measure. Most observers agree that the therapeutic weapon of choice in combating this disease is the intravenous use of an arsenical preparation. Improvement usually comes after the first or second injection in our experience.[2] This experience has been confirmed recently by Ewert and Hoffman.[5] Occasionally a third or fourth injection may be required but this is not the rule. In my experience small doses of neoarsphenamine are just as efficacious as the larger doses, and I recommend 0.2 gm. for the first dose, followed in four to five days by a dose of 0.3 gm., with subsequent doses, if needed, given at the same interval and of the same size. Because of the excellent results which usually follow the administration of the arsenicals intravenously, it has been supposed that a spirochete might be the etiologic agent. However, Wildbolz[7] has called attention to the fact that the Wassermann reaction on the blood for syphilis and examination of the urine for the presence of spirochetes by dark-field illumination always give negative results.

Having discussed the most important therapeutic procedure, I wish now to say a few words concerning what I believe to be a definite adjunct to treatment and in some cases a positive requirement. I always hesitate to suggest foci of infection as the reason for a urologic disorder. This hesitancy exists because of the difficulty of proof and also because I do not wish to encourage the indiscriminate removal of teeth or tonsils for infections of the urinary tract. However, in a large group of these cases in which initial improvement has been brought

about by the administration of the arsenicals, removal of any foci has produced a definite exacerbation of the symptoms with an increase in the urinary findings. This observation certainly seems to suggest a relationship. Furthermore, in a few patients who have recurrent trouble even after taking arsenicals, removal of foci has brought about a complete cure. Foci are important and should be borne in mind. The teeth and tonsils should be investigated carefully; the prostate gland should be examined and massaged if infection is found, or the cervix uteri should be carefully checked and treatment instituted if necessary.

Report of Case

A white man, twenty-one years of age, registered at the clinic November 1, 1943. His main complaint was burning and frequent urination, hematuria, and extreme dysuria of four months' duration. Examination at home had revealed a bladder of small capacity, severe cystitis and definite reduction of renal function as shown by the excretory urogram. Early hydronephrosis was noted on both sides. Staining of the urinary sediment was reported to show acid-fast bacilli. Inoculations of guinea-pigs had not been made.

At the time of examination at the clinic the patient was wearing a urinal because of the extreme frequency and urgency. His tonsils were grossly infected and exuding pus. There was definite suprapubic tenderness and his prostate gland was tender on rectal examination. The genitalia were otherwise normal. The significant laboratory data revealed pus, grade 4, and erythrocytes, grade 4, in the urinary sediment but all the staining and cultures of the urine failed to reveal the usual invading organisms as well as the acid-fast organisms of tuberculosis. Visualization of both kidneys was delayed in the excretory urogram and there was dilatation of the pelvis, calices and ureters, grade 2. Cystoscopic examinations under pentothal sodium anesthesia revealed acute diffuse cystitis, grade 4, which was not suggestive of tuberculosis.

Continuous vesical lavage with 1:10,000 of silver nitrate was begun and continued for one week. The patient then was dismissed from the hospital and local treatment as described previously was carried out in the office twice daily. He was given one injection of neoarsphenamine and this medication brought about real improvement in his condition. Five days later a second injection was given with further improvement but unfortunately toxic erythema developed and further treatment of

this nature was impossible. His situation remained about the same for another week and tonsillectomy was advised. This was done and was followed by a definite exacerbation of all his vesical symptoms for two or three days. Local treatment was continued and in one week following tonsillectomy all symptoms had disappeared. The urine continued to show pyuria, grade 3, but with lavage and prostatic massage, the urine cleared up and the patient was dismissed as cured. An excretory urogram just before dismissal was entirely negative and cystoscopic examination gave negative results except for a few patches of redness over the trigone of the bladder.

Comment

The main concern of this paper is a condition which is becoming better known as time goes on. However, the frequency with which it is missed seems ample justification for considering it in detail. Careful studies of the urinary sediment and cultures of the urine, when possible, are of utmost value and should be carried out in all cases. The differential diagnosis between amicrobic pyuria and tuberculosis must be made with care. This latter condition presents many problems in its diagnosis and should ever be present in the mind of the examining physician.

In the treatment of amicrobic pyuria, the usual chemotherapeutic compounds that are so efficacious in combating the ordinary infections of the urinary tract are of little value. Local treatment gives only palliation, but the intravenous administration of arsenical compounds is almost specific. Along with this, however, I should like to make a plea for the appreciation of the part which foci of infection play in many of these cases. Permanent cure will frequently be impossible unless existing foci are eradicated and the teeth, tonsils, prostate gland, and uterine cervix are the most common.

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BIOLOGICAL DIFFERENTIATION OF BENIGN AND MALIGNANT GROWTHS*

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ONE phase of an extensive constitutional study under progress in this laboratory has been an investigation of spontaneous neoplasia in the rabbit and, as a result of routine clinical and pathological examinations carried on over a period of years, a considerable series of tumors has been found. Cancers of the breast and of the uterus have occurred with the greatest frequency and have been subjected to more thorough study than the less common tumors of other organs. It is encouraging that in morphology, mode of development and biological characteristics, these growths bear a much closer resemblance to human cancers than do the corresponding tumors under study in other animal species.

A characteristic feature of the breast and uterine cancer is the occurrence of a well defined developmental history (Greene and Saxton 1938,[1] Greene 1939[2]). They do not arise as a sudden transition of normal cells but, on the other hand, represent the final step in a progressive developmental process during the course of which the primary neoplastic focus passes through successive stages of anaplastic cellular change, local tissue invasion, foreign tisssue invasion and eventually metastasis. Transplantation experiments utilizing the anterior chamber of the eye as an inoculation site showed that the tumors could not be transferred to normal animals during stages of anaplastic cellular change or of local tissue invasion but could be transferred to normal animals during the stage of foreign tissue invasion (Greene 1940[3]). It was, therefore, concluded that anaplastic cellular change or local tissue invasion in the primary growths of these tumors did not constitute evidence of autonomy but rather stages in the development of autonomy, the final attainment of which was only evidenced by foreign tissue invasion.

In contrast to the failure of transfer to normal animals during

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stages prior to foreign tissue invasion, it was found that at such stages the developing tumors could be successfully transplanted to animals bearing spontaneous growths. This finding suggested that special factors were present in the spontaneous hosts but absent in normal animals and the nature of the endocrine changes constantly found in tumor bearing animals indicated that one of these factors might be an abnormal secretion of estrone. It was subsequently found that dependent tumors survived and grew in estrinized animals, whereas early death of the transplants occurred in normal animals used as controls and it was concluded that the constitutional status incident to an abnormal secretion of estrone was one of the factors essential to the continued growth and development of the tumors (Greene 1940[4]).

Cancers of the breast and uterus have been carried for many serial generations in normal rabbits and experimental investigations have been concerned with attempts to alter malignancy and to determine the immunological status of animals during different stages of tumor growth (Greene 1939,[5] 1940[3]). The tumors have also been successfully transplanted to foreign species, including guinea pigs, hens, goats, sheep and hogs, by means of the anterior chamber technique (Greene 1941[6]). The tumors receive a blood supply from the alien host and grow progressively. The cells of the transplant, however, are descendants of the original tumor and not derivatives of the foreign species.

The anterior chamber has also been used for the heterologous transplantation of mouse tumors and it has been found that in this species tumors undergo the same biological phases of dependency and autonomy observed in the development of rabbit cancer.

It has also been possible to transplant human tumors to lower species using this route of inoculation (Greene 1942,[7] 1944[8]). A considerable series of human tumors have been tested and it has been found that successful transplantation to normal animals could only be performed after the occurrence of foreign tissue invasion and it was concluded that, in human as in rabbit tumors, this stage marks the attainment of autonomy.

An interpretation of the significance of the capacity of cancer tissue to grow in alien hosts necessitated a more accurate definition of the limits of heterotransplantability and a series of experiments was instituted to determine whether or not this power was shared by other tissues. Benign tumors, normal adult tissue and normal embryonic tissue

(Greene 1943[9]) have been tested with respect to this property as well as to the ability to survive and grow in other environments and the results are presented in the accompanying chart.

TRANSFER

Tissue	*Autologous*	*Homologous*	*Heterologous*
Normal Adult	+	+	—
Normal Embryonic	+	+	+
Benign Tumor	+	—	—
Cancer	+	+	+

The property of heterologous transplantability accents the relationship between cancer and embryonic tissue and suggests the possession of a common attribute that differentiates them biologically from other normal and pathological tissue states.

The primary conclusions indicated by the findings described in this abstract are first, that the rabbit cancers are not simply local tissue diseases but, on the other hand, represent local manifestations of a generalized constitutional disorder and, second, that in the rabbit the primary neoplastic focus is not a cancer and that before becoming a cancer it must undergo a process of progressive evolutionary development. Development to cancer will not take place in normal animals but is dependent on a special constitutional status which may be evoked experimentally by the administration of estrogenic substances. Both human and mouse cancers undergo a similar developmental course in their advance to cancer and in all of the species studied this course is characterized by dependent and autonomous phases.

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